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TOBACCO INDUSTRY RESEARCH COMMITTEE
150 EAST FORTY SECOND STREET NEW YORK 17, N. Y.

Cf #508
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Application For Research Grant

Date: July 19, 1957

1. Name of Investigator: William O. Russell, M.D.

2. Title: Pathologist-in-Chief, M.D. Anderson Hospital and Tumor Institute; Professor of Pathology, University of Texas Postgraduate Medical School

3. Institution & Address: M.D. Anderson Hospital and Tumor Institute
6723 Bartner Drive
Houston 25, Texas

4. Project or Subject: Investigation, by whole organ subserial sections, of the possible carcinogenic effect of androgens and estrogens upon the respiratory mucous membrane; correlation with studies of the respiratory tract of patients with bronchogenic carcinoma.

5. Detailed Plan of Procedure (Use reverse side if additional space is needed):

(See Continuation sheets 1 to 5 for presentation of subject and Detailed Plan of Procedure.)

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Introduction

The herein proposed investigations of the effects of hormones upon the human respiratory tract by whole organ subserial sections would be coordinated with a pulmonary cytology project currently being activated at the M.D. Anderson Hospital and Tumor Institute by the Field Investigations and Demonstrations Branch of the National Cancer Institute. The whole organ subserial technique to be utilized in the proposed correlative study was adapted for investigation of the human respiratory tract through the assistance of a grant from the Tobacco Industry Research Committee for anatomic-pathologic study of lungs.

One of the areas to be investigated in the pulmonary cytology project at this institution is the effect of sex hormones upon the cells in bronchial secretions of patients under treatment for cancer of the breast and prostate. Concomitantly, the pulmonary secretions of patients with lung cancer, as well as of patients from the clinic who have had a primary lung cancer removed, will be studied. The coordination of these two studies with each other and with studies of the pathologic changes in primary carcinoma of the lung and in the respiratory tract of patients who have received hormone therapy for carcinoma of the breast and prostate, by the method herein described, would provide an unique opportunity for the correlation of morbid anatomy with exfoliative cytology.

a) Specific Aim:

The study of the possible influence of sex hormones upon the rate of growth, replacement and morphology of the mucosal cells of the respiratory tract in relation to carcinogenesis.

b) Discussion of Problem:

One of the most significant advances in the field of cancer has been the recognition of the fact that the continued growth and development of certain types of neoplastic cells are influenced by sex hormones. In view of their proved beneficial effect upon cancer of the breast and of the prostate, the sex hormones have become established as a part of the treatment of these two tumors.

It is not known whether the sex hormones produce any effect upon the cells of the respiratory tract. From the following facts, however, it would seem that the sex hormones might influence the rate of growth, replacement and morphology of mucous membrane cells and play some role in the development therein of neoplastic changes:

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(1) Adult male and female voices are characteristically different, the alteration in the male voice taking place at puberty. (2) The benign neoplastic conditions of juvenile papillomatosis of the larynx and juvenile nasal angiofibroma are restricted to the time of life when the sex hormones are assuming a new and heightened effect in the body. (3) Juvenile laryngeal papillomatosis has been reported to respond to treatment with sex hormones. (4) Following androgen therapy for breast cancer, gross changes in the laryngeal mucosa have been observed clinically. (5) The higher incidence of lung cancer in men than in women suggests that hormones may play some part in the pathogenesis of the disease.

Patients with metastatic breast cancer and almost all of those with prostate cancer at some time during the course of their disease receive large amounts of sex hormones, frequently in combination with ablation of hormone producing or stimulating tissues, such as ovaries, testes, adrenal glands and pituitary gland. As a result, the body tissues are subjected to a most abnormal hormonal change. These patients, therefore, would be excellent subjects for investigation and evaluation of the effects of hormones upon the cells of the human respiratory tract.

In the previously mentioned pulmonary cytology project at the M.D. Anderson Hospital and Tumor Institute, which is to be supported by the National Cancer Institute, bronchial secretions of patients with cancer of the breast and of the prostate who receive hormone therapy will be studied before, during and after treatment. In addition, control studies will be made of the secretions of individuals who do not receive hormones. Histopathologic examination of the respiratory mucous membranes of these subjects at autopsy would provide the ultimate opportunity for correlation of the morphologic changes with the cytologic findings in the bronchial secretions during hormone therapy. Although in most cases months or years would elapse between the hormone therapy and the necropsy, it may be assumed that careful studies, as herein planned, would permit the detection of any cellular morphologic changes which would be considered significant in the pathogenesis of lung cancer.

It is reasonable to assume a long latent period for bronchogenic carcinoma in relation to any exogenous and endogenous etiologic agents. If inhalation of the an exogenous substance, such as tobacco smoke, is a primary factor, and some hormone a co-factor, the period of latency from the first contact with the agents could be estimated as from 30 to 35 years. The fact that the disease reaches its peak incidence in persons around the age of 50 would substantiate this view. It has been shown that the latent period of pulmonary carcinoma arising from such known carcinogens as chromates and asbestos is much shorter. Relatively short periods of abnormal hormonal stimulation could reasonably incite potentially cancerous changes detectable by the herein contemplated study. These could explain many pulmonary cancers and possibly their high incidance in men.

c) Study Material:

During 1955 and 1956 the following cases were available for study at the M.D. Anderson Hospital and Tumor Institute:

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Site	New Cases	No Previous Surgery	Deaths	Autopsies
Prostate	64	42	8	7
Lung	124	107	27	23
Breast	275	138	17	6
Totals	463	287	52	36

During 1957 and 1958 the institution is expected to reach the limit of its clinical capacity; therefore, a material increase in the number of patients admitted for cancer of the breast, prostate and lung is anticipated. In addition, cases will be available through other clinical activities in the Texas Medical Center connected with the "cytology project." Within four years a sufficient number of cases can be collected to permit definite conclusions as to any pathologic changes in the respiratory tract of possible etiologic significance in pulmonary carcinoma.

The follow-up services of the Anderson Hospital Clinic can provide a larger number of autopsies than listed. Only a small percentage of patients die in the hospital, yet over 90 per cent are residents of Texas. With the cooperation of pathologists in other localities, lung specimens from those patients who have been under hormone therapy and cytologic observation, but have not died in this hospital, may be obtained from hospitals throughout the state. If no local pathologist is available in such cases, a member of the pathology staff of this institution would be sent to conduct the autopsy.

5. Detailed Plan of Procedure:

A) Whole organ studies would be made of the larynx, trachea and bronchial tree of autopsy subjects following death from cancer of the breast and of the prostate, for which hormone therapy had been given.

B) For comparative purposes, lungs of patients who have died from bronchogenic epidermoid carcinoma would be studied in like manner. The results reported by the Tobacco Industry pathology study group failed to show a striking association of such pathologic changes as squamous metaplasia or atypical hyperplasia with carcinoma; the proposed investigation, however, would be carried out in greater detail and thus would afford an opportunity for a more thorough and finite evaluation of this problem.

C) For control cases, the respiratory systems of autopsy subjects between the ages of 45 and 55 would be studied following death from diseases other than cancer. Cases of this type are readily available from the Medical Examiner's office in Houston.

D) All the case studies would include a carefully taken history with reference to tobacco smoking, for evaluation in the ultimate results.

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E) Subserial whole organ technique for study of the respiratory tract.- The procedure described below has been developed at the M.D. Anderson Hospital and Tumor Institute for studying the human respiratory tract at autopsy.

The larynx, trachea and lungs are removed en bloc and fixed in 10 per cent neutral formalin. The tracheobronchial tree is filled with formalin to insure the most rapid fixation of the mucosal tissues before total immersion. After seven to ten days of fixation in the formalin, the specimen is dissected and the sections are taken as follows:

The larynx is detached from the trachea and sectioned in the frontal plane. At approximately 3 cms. above the bifurcation, the trachea is cut transversely and divided into five or six rings for sectioning. The remaining trachea with the bifurcation and the two main stem bronchi are detached as a separate specimen for blocking. The detached lungs are decorticated by slicing off the excess parenchyma in layers with a knife, so as to preserve the major and minor bronchi as well as possible. Each lung specimen so prepared measures approximately 2.5 x 8 x 4 cms. (See Exhibit A, plate 1, showing specimens prepared for sectioning.)

The specimens are processed by the routine paraffin technique, each step being somewhat lengthened to accommodate the large tissue mass. After the tissues are embedded in paraffin, sections 8 microns in thickness are made on a Spencer sliding microtome at 1 mm. intervals and stained by hematoxylin and eosin, then mounted on glass slides of either 2 x 3 or 3 x 4 inch dimensions. By this method, an average of 35 slides are obtained from the larynx, and 10, 15 and 20 slides from each of the other specimens, respectively.

The linear surface of mucosa provided by the above described technique is, roughly, as follows:

	Average Number Sections	Cm. of Mucosa
Larynx	28	620
Trachea	44	900
Bifurcation and Primary Bronchi	15	167
Hilar Tissue and Principal Bronchi (Rt.	22	5,000
Hilar Tissue and Principal Bronchi (Lt.	24	6,300
Totals	133	12,987

The above figures, showing an estimated 133 sections on each case, with an estimated 12,987 cms. of respiratory tract mucosal surface available for study, give some idea of the completeness of the examination and its usefulness in the detection and study of pathologic changes in the respiratory tract. (For pictorial evaluation of the whole organ sections, see Exhibit A, plates 2 and 3.)

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Budget Analysis:

Budget Plan

Salaries	$14,~~000~~.00 (004.00)
Expendable supplies . . .	2,000.00
Permanent equipment . . .	1,400.00
Overhead	1,488.00
Travel	1,200.00
Total	$20,~~088~~.00 (092.)

a) Personnel:

Itemized Salaries

Senior pathologist, part time	$ 6,000.00
Research technologist, II (histology)	4,404.00
Senior clerk-typist, part time	1,512.00
Research technologist (histology), half time	1,824.00
Social Security Tax	~~260.00~~ 264.00
Total	$14,~~250.00~~ 14[illegible].00

1) Senior pathologist, part time: A pathologist at an assistant or associate level would be necessary for the proper execution of this project. Thorough qualification in pathologic anatomy would be a prerequisite, since the study and interpretation of many thousands of sections would be the major professional assignment of the project. It is estimated that one-third or more of the time of such a person would be devoted to this work.

2) Research technologist, II (histology): The entire program would be dependent upon the preparation of whole organ sections, for which specialized training and skill in the various techniques is essential on the part of the medical technologist.

3) Senior clerk typist, part time: Typing and clerical assistance would be necessary for obtaining data on cases to be studied, for preparation of forms, correspondence regarding outside information on patients and autopsy studies, and for preparation of reports and papers for publication.

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4) Research technologist (histology), half time: It is estimated that half the time of a superior tissue technologist with some experience in whole organ section technique would be necessary. This person would work with and under the Research Technologist, II.

b) Expendable supplies.- In the preparation of whole organ sections, supplies are consumed at a rapid rate. The slides and cover slips are custom cut. Reagents are used in large quantities, and considerable numbers of staining receptacles, miscellaneous glassware and bottles are required.

c) Permanent equipment.- Two low power scanning microscopes of the Zeiss cytoplast type would be needed. The pathologist would utilize one in scanning the sections, and the technologists would use one in staining procedures for evaluation of intensity of stains and general excellence of preparation. The laboratory has all other permanent equipment necessary to produce whole organ sections ~~and~~ as outlined.

d) Travel.- Travel funds would be used by persons engaged in this program for the purpose of consulting with others regarding problems related to the project and to report results of studies at scientific meetings. It would also be necessary for staff members of the Department of Pathology to travel to other parts of Texas to perform autopsies on selected patients following death in their local hospitals. To illustrate the expense involved in intrastate travel in Texas, the cost of a round trip plane passage between Houston and El Paso is $96.25.

It is anticipated that the consumable supply and travel expenses will increase after the first year as the program becomes fully activated. This will be offset by a reduction in permanent equipment expense after the first year.

10. Relationship of Proposed Study to Pulmonary Cytology Project:

A cooperative research program between the M.D. Anderson Hospital and Tumor Institute and the Field Investigations and Demonstrations Branch of the National Cancer Institute is being activated in Houston for the study of pulmonary cytology. The objectives of the project are as follows:

a) Cytologic examination of sputum and/or bronchial washings to determine general smear characteristics and specific cellular morphology.

b) Development and investigation of improved methods for collection of sputum specimens for cytologic study. This will include both chemical and mechanical methods.

c) Development and investigation of methods of preservation, processing and staining of sputum and/or bronchial washings.

d) Evaluation of screening methods for examination of prepared specimens.

One of the initial projects will be a study of the effects of hormone therapy, given to patients for mammary and prostatic cancer, upon the cells in secretions from their respiratory tracts, as well as cellular changes in secretions from the respiratory tracts of normal subjects. This field of exfoliative cytology is untouched. Such a study will provide an unusually complete background for the whole organ investigations of the respiratory system of cancer subjects included in the proposed project.

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6. Budget Plan:

Salaries	~~$14,665.00~~ 984
Expendable Supplies	2,000.00
Permanent Equipment	1,400.00
Overhead 7.1%	1,488.00
Other	1,200.00
Total	~~$20,693.00~~ 092.

(See Continuation sheets 6 and 7.)

7. Anticipated Duration of Work:

Four years will be needed to collect a sufficient number of cases to be of significance in the evaluation of this problem.

8. Facilities and Staff Available:

New, completely equipped laboratories for anatomic and clinical pathology are available in a 310 bed center for cancer education, research and treatment. The staff of the Department of Pathology consists of six senior pathologists and seven fellows. For the past seven years the Department of Pathology has been working on the development of whole organ subserial paraffin sections. It will be possible a to obtain qualified technologists through the training program for histologic technologists at the M.D. Anderson Hospital and Tumor Institute.

9. Additional Requirements:

None.

10. Additional Information (Including relation of work to other projects and other sources of supply):

(See Continuation sheet 8.)

Signature **/s/ William O. Russell**
Director of Project

/s/ Joe E. Boyd, Jr.
Business Officer of the Institution

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